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U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPRO-PRIATE
	AA						
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FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION Yes	TRANSLATION No*
	AL	644 177	7/9/97	Europe				
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OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

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Synthesis of Primary Amines Using Potassium 1,1,3,3-Tetramethyldisilazide as Aminating Agent of Alkyl Halides

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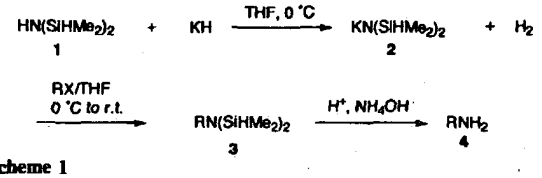
A one-pot synthesis of various primary amines is described. Potassium 1,1,3,3-tetramethyldisilazide, prepared from 1,1,3,3-tetramethyldisilazane and potassium hydride, reacts with alkyl bromides, iodides, tosylates, benzylic chlorides, and allylic chlorides to give the corresponding *N,N*-bis(dimethylsilyl)amines in high yields. Subsequent deprotection of the dimethylsilyl group was performed under mildly acidic conditions to afford primary amines. This method was also applied to the preparation of aminomethylated cross-linked polystyrene.

Alkylation of protected ammonia by alkyl halides is one of the most useful procedures for the preparation of primary amines. The existing methodology employs mainly protected ammonia in the form of potassium phthalimide (Gabriel synthesis)[1] and hexamethylenetetramine (Delépine reaction)[2] as the aminating agent. Alternatives to the Gabriel synthesis involve treatment of the halide with the strong base guanidine[3] or the sodium salt of diphenylphosphinamide[4] followed by hydrolysis to give primary amine. Although these reactions can be performed under mild conditions, the final deprotection step still requires somewhat drastic conditions. Some modified Gabriel syntheses have been reported for the improved deprotection conditions.[5]

On the other hand, the trialkylsilyl group has been widely used as a protecting group for amines, including primary amines.[6] Silyl derivatives provide satisfactory protection under a variety of reaction conditions.[7] Deprotection of silylamines to give the free amine can be achieved under very mild acidic conditions.[8] Thus *N,N*-disilylamines are potential candidates as *N,N*-bis-protected nitrogen nucleophiles if they have enough nucleophilicity. Primary amines can be easily obtained from deprotection of the *N,N*-disilylamines. Silazanes and their metal amides, however, have been used extensively as a base in many organic reactions. For example, lithium hexamethyldisilazide is known to be a strong non-nucleophilic base that is a useful reagent for the generation of enolates.[9] The use of lithium hexamethyldisilazide for reactions with alkyl halides often results in proton abstraction of the substrates rather than nucleophilic substitution reaction. Sodium bis(trimethylsilyl)amide has been reported to react with alkyl bromides or iodides to give the desired primary amines in moderate chemical yield.[10] However, side reactions caused by the highly basic bis(trimethylsilyl)amide anion could not be avoided. Hosomi et al. reported that potassium 2,6-disilapiperidine, prepared via a five-step synthesis from allyltrimethylsilane, could be *N*-alkylated with alkyl halides under vigorous reaction conditions to give the corresponding primary amines after acid hydrolysis in refluxing aqueous 1 M hydrochloric acid for 8 hours.[11] Recently, Murai et al. improved this low nucleophilicity of lithium hexamethyldisilazide by using silver iodide as an additive.[12] *N,N*-Bistrimethylsilylated allylic amines have been prepared from their chlorides by this method.

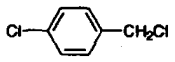
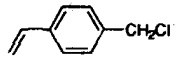
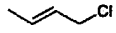
We have discovered that potassium 1,1,3,3-tetramethyldisilazide (**2**) is an efficient silyl-protected nitrogen nucleophile which does not produce any additives in amination reactions of alkyl halides (Scheme 1). Potassium disilazide **2** has less hindered silyl groups, enhancing its nucleophilic properties at the nitrogen atom. Several types of alkyl halides have been aminated with this reagent in high yield under mild reaction conditions. We now wish to report the simple preparative route to primary amines from alkyl halides by the use of **2**.

The disilazide **2** was readily prepared from commercially available 1,1,3,3-tetramethyldisilazane (**1**) with potassium hydride in tetrahydrofuran (THF). Hexyl bromide reacted with **2** between 0 °C and room temperature to form *N,N*-bis(dimethylsilyl)hexylamine (**3a**) which could be isolated by distillation. Under mildly acidic conditions, cleavage of the N–Si bond was completely achieved to afford hexylamine quantitatively. Primary amines were also obtained by direct hydrolysis of the reaction mixture without isolation of any silylamine intermediates. Yields of silylamines and primary amines are shown in Table 1. Primary bromides reacted smoothly with **2** (entries 1 and 2), while a secondary bromide gave only a low yield of the corresponding amine. In the case of phenylethyl bromide, the main product was styrene since elimination occurred preferably to substitution. For the same reason the desired primary amine was also not obtained from a tertiary bromide. The nucleophilicity of **2** was not enough to react with bromobenzene or hexyl chloride. Highly reactive chlorides such as benzylic chlorides and allylic chlorides afforded the corresponding primary amines in high yields. However, all our attempts to synthesize the corresponding amines from active methylene compounds such as bromoacetates, chloroacetates and chloroacetaldehyde failed. In these cases **2** showed its basic character, causing undesired side reactions. Several metal disilazides other than **2** have been tested as the aminating agent of benzyl chloride. Potassium hexamethyldisilazide, prepared from hexamethyldisilazane and potassium hydride, was used under the same reaction conditions employed for **2** but the yield of benzylamine obtained was low (24%). The reactivity of sodium hydride is too weak to generate the sodium amide of **1**, in contrast to that of potassium hydride. Thus combination of sodium hydride and **1** failed to give benzylamine (entry 6). Metal amides of cyclic silazanes appear to be less hindered nitrogen nucleophiles than those of hexamethyldisilazane. Reaction of potassium amides of cyclic silazanes with benzyl chloride gave benzylamine after hydrolytic work-up. Generation of two nitrogen anions in a cyclic silazane resulted in the formation of an insoluble amide species that caused low conversion of benzyl chloride to the corresponding silylamine (entry 9).



Scheme 1

Table 1. Preparation of Primary Amines from Halides using Potassium Silazide

Entry	Silazane	Halide	Yield (%) Silylamine (3)	Yield (%) Primary Amine (4)
1	1	$Me(CH_2)_5Br$	3a 85	4a 83
2	1	$Me(CH_2)_7Br$	3b 90	4b 87
3	1	$Me(CH_2)_5OTs$	-[a]	4a 85
4	1	$Me(CH_2)_7I$	-[a]	4b 71
5	1	$PhCH_2Cl$	3d 89	4d 88
6	1[b]	$PhCH_2Cl$	-[a]	4d 0
7	HMDS[c]	$PhCH_2Cl$	-[a]	4d 24
8	HMCTS[d]	$PhCH_2Cl$	-[a]	4d 74
9[e]	HMCTS[d]	$PhCH_2Cl$	-[a]	4d 48
10	OMCTS[f]	$PhCH_2Cl$	-[a]	4d 45
11	1		-[a]	4e 80
12	1		-[a]	4f 83
13	1		3g 88	4g 90
14	1		3h 91	4h 89
15	1		3i 92	4i 91

[a] Silylamine was not isolated. [b] NaH was used as metal source.
[c] Hexamethyldisilazane. [d] Hexamethylcyclotrisilazane.
[e] [HMCTS] : [KH] : [Benzyl chloride] = 1 : 2 : 2.
[f] Octamethylcyclotetrasilazane.

From above discussions of the disilazides used, **2** is the most suitable reagent for the amination of alkyl halides and tosylates. Various primary amines are obtained conveniently by this one-pot synthesis. This facile amination reaction was also applied to the preparation of cross-linked polymeric amines. In spite of the heterogeneous reactions, insoluble chloromethylated polystyrene cross-linked with divinylbenzene was quantitatively converted to aminomethylated polystyrene, which is a useful supporting material for peptide synthesis.[13] Although benzyl chloride was aminated by lithium hexamethyldisilazide–silver iodide reagent,[14] it was difficult to remove the deposited silver salt from the insoluble polymeric amine.

In conclusion, primary alkyl bromides, iodides, and tosylate, and allylic and benzylic chlorides react with **2** to give the corresponding *N,N*-bis(dimethylsilyl)amines which are easily hydrolyzed under mildly acidic conditions to produce their primary amine salts in high overall yields. This one-pot synthesis of silyl-protected primary amines and their free amines is a useful tool for amine synthesis. We are currently exploring the Michael additions of this new nitrogen-protected nucleophile.

Hexamethyldisilazane, 1,1,3,3-tetramethyldisilazane, hexamethylcyclotrisilazane, and octamethylcyclotetrasilazane were purchased from Shin-Etsu Silicone Co. Tetrahydrofuran (THF) was freshly distilled over benzophenone ketyl under Ar before use. Potassium hydride purchased from Aldrich Co. was used as it was. 4-Vinylbenzyl chloride was a gift from Seimi Chemical Co. Microanalyses were obtained using a YANACO MT-3 CHN CORDER. IR spectra were recorded on a JEOL JIR-7000 FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-GX270 spectrometer. All reactions were carried out under an Ar atmosphere. Satisfactory microanalyses were obtained for compounds **3a, 3b, 3d, 3g–i**: C ± 0.05; H ± 0.36; N ± 0.08.

***N,N*-Bis(dimethylsilyl)benzylamine (3d); General Procedure:**
In a 100 mL pre-dried round-bottom flask was placed potassium hydride (0.44 g, 11 mmol) in THF (0.5 M) under Ar and **1** (1.74 mL, 10 mmol) was added dropwise at 0 °C. The mixture was then stirred for 30 min to generate **2**. Benzyl chloride (1.15 mL, 10 mmol) was added slowly to the mixture and stirring continued at 0 °C for 1 h and for a further 1 h at r.t. Salts were filtered under Ar and the filtrate was evaporated under reduced pressure to yield a crude oil which was purified by bulb-to-bulb distillation (oven temperature 135 °C/1 Torr) to furnish **3d**, yield 1.99 g (89%).
IR (neat): ν = 2160, 1260 cm^{-1}.
^{1}H NMR ($CDCl_3$/TMS): δ = 0.14 (d, 6H, J = 3.4 Hz); 4.09 (s, 2H); 4.51 (m, 2H); 7.28 (m, 5H).
^{13}C NMR ($CDCl_3$/TMS): δ = −0.68, 49.3, 126.4, 127.1, 128.1, 142.8.

N,N-Bis(dimethylsilyl)hexylamine **(3a)**: bp 120 °C/5 Torr.
IR (neat): ν = 2160, 1250 cm^{-1}.
^{1}H NMR ($CDCl_3$/TMS): δ = 0.11 (d, 6H, J = 3.4 Hz); 0.87 (t, 3H, J = 7.0 Hz); 1.15–1.35 (m, 8H); 2.75 (t, 2H, J = 8.5 Hz); 4.39 (m, 2H).
^{13}C NMR ($CDCl_3$/TMS): δ = −0.4, 14.0, 22.7, 26.8, 31.7, 34.3, 46.2.

N,N-Bis(dimethylsilyl)octylamine **(3b)**: bp 120 °C/1 Torr.
IR (neat): ν = 2160, 1250 cm^{-1}.
^{1}H NMR ($CDCl_3$/TMS): δ = 0.14 (d, 6H, J = 3.4 Hz); 0.88 (t, 3H, J = 7.3 Hz); 1.12–1.45 (m, 12H); 2.77 (t, 2H, J = 8.6 Hz); 4.42 (m, 2H).
^{13}C NMR ($CDCl_3$/TMS): δ = −0.4, 14.1, 22.7, 27.2, 29.3, 29.7, 31.9, 34.4, 46.2.

N,N-Bis(dimethylsilyl)allylamine **(3g)**: bp 60 °C/15 Torr.
IR (neat): ν = 2160, 1250 cm^{-1}.
^{1}H NMR ($CDCl_3$/TMS): δ = 0.13 (d, 6H, J = 3.4 Hz); 3.43 (m, 2H); 4.43 (m, 2H); 4.98 (dd, 1H, J = 10.3 and 2.0 Hz); 5.09 (dd, 1H, J = 17.1 and 2.0 Hz); 5.70–5.82 (m, 1H).
^{13}C NMR ($CDCl_3$/TMS): δ = 0.5, 44.7, 113.7, 139.6.

N,N-Bis(dimethylsilyl)crotylamine **(3h)**: bp 90 °C/15 Torr.
IR (neat): 2160, 1250 cm^{-1}.
^{1}H NMR ($CDCl_3$/TMS): δ = 0.06 (d, 6H, J = 3.4 Hz); 1.58 (d, 3H, J = 7.7 Hz); 3.31 (d, 2H, J = 7.7 Hz); 4.36 (m, 2H); 5.23–5.50 (m, 2H).
^{13}C NMR ($CDCl_3$/TMS): δ = −0.5, 17.5, 47.3, 124.8, 132.7.

N,N-Bis(dimethylsilyl)-1-methylallylamine (**3i**): bp 90°C/15 Torr.
IR (neat): $\nu = 2160, 1250\ cm^{-1}$.
^1H NMR ($CDCl_3$/TMS): $\delta = 0.14$ (d, 6H, $J = 3.4$ Hz); 1.68 (s, 3H); 3.33 (s, 2H); 4.45 (m, 2H); 4.79 (s, 1H); 4.91 (s, 1H).
^{13}C NMR ($CDCl_3$/TMS): $\delta = -0.7, 20.2, 51.5, 109.9, 146.1$.

Preparation of Primary Amines without Isolation of Silylamine Intermediates; General Procedure:
In a 200 mL pre-dried round-bottom flask was placed potassium hydride (2.2 g, 55 mmol) in THF (0.5 M) under Ar and **1** (8.7 mL, 50 mmol) was added dropwise at 0°C. The mixture was then stirred for 30 min to generate **2**. Benzyl chloride (5.75 mL, 50 mmol) was added slowly to the mixture and stirring continued at 0°C for 1 h and for a further 1 h at r.t. After the reaction was quenched with aq NH_4Cl solution (25 mL), 0.5 N HCl (20 mL) was added. The mixture was neutralized with NH_4OH and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and evaporated to give the crude benzylamine, which was then purified by distillation, yield 88%, bp 90°C/12 Torr. (Ref[15], bp 185°C).

Preparation of Aminomethylated Cross-Linked Polystyrene:
Chloromethylated polystyrene resin cross-linked with divinylbenzene (2% divinylbenzene, 2.23 mequiv of Cl/g, 2.25 g), prepared by trioxane–chlorotrimethylsilane method,[16] was treated with **2** (10 mmol) in dry THF (15 mL) at r.t. for 10 h. The polymer suspension was filtered and the residue was washed with 50 mL portions of THF, THF–water, THF–0.5 N HCl, THF, THF–NH_4OH, THF–water, and MeOH, successively. After drying in vacuo at 40°C overnight, 2.15 g (100%) of polymer was obtained. Nitrogen analysis indicated a content of amino group in the polymer corresponding to 2.33 mequiv of N/g. IR (KBr): peak absent at 1265 cm^{-1} for chloride precursor, peaks present at 3410, 1098 cm^{-1}.

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